J Infect Chemother (2011) 17 (Suppl 1):80–83
DOI 10.1007/s10156-010-0145-6

GUIDELINES

Chapter 2-5-3c. Anaerobic infections (individual fields): skin and soft tissue infections—foot infection

Pathogenesis

Foot infections are actually skin and soft tissue infections of the lower extremities. Infection of the dermis is categorized as acute dermatitis and that of subcutaneous tissues as soft tissue infection (cellulitis). In this section, the latter is summarized. For cases in which gas bubbles are recognized in lower extremity tissues on X-ray examination, and when bony changes are seen, i.e., gas gangrene and necrotizing fasciitis, which involve infection invading the fascia and the muscle layer, and osteomyelitis, are addressed in other sections.

Foot infections often present with a past history of contamination with bacteria due to factors such as injury, burn, ulcer, tinea pedis, ingrown nail, insect bites, surgery, etc., but in many cases the causes are unclear. The infected lesion in the early stage shows diffuse redness with heat sensation, a locally swollen surface and local tenderness. Foot infections commonly occur in the area ranging from the foot to the leg. The area spreads to upper part with the spread of inflammation. When the inflammation is superficial, it is demarcated (the margin is distinct) and protuberance is frequently associated with inflammation. This superficial inflammation shows localized small eruptions, but map-like erythema is quite common. Expansion and progression of the infection lead to abscess formation. In cases in which the infected lesion expands rapidly, the prognosis is poor. When the infection spreads via lymphatic vessels from the infected lesion, red erythema spreads craniad toward the inguinal region. With expansion of the infected lesion, systemic signs and symptoms such as pyrexia, leukocytosis, high C-reactive protein (CRP) levels, and so on, appear (Table 1).

Risk factors for foot infection are impaired immune responses at local sites and systemically, blood flow disturbances, lymph congestion and the existence of foreign bodies.

Diabetes mellitus (DM) is clearly a major risk factor. Since immunological competence is decreased by persistent hyperglycemia, microscopic infected lesions become refractory, and the infection tends to accelerate without treatment of diabetic neuropathy. With regard to the characteristics of DM-induced infection, the association of arteriosclerosis obliterans, etc. with the infection contributes to the development of tissue necrosis and ulceration, thereby increasing the severity of the infection.

Another risk factor is blood flow disturbances in the peripheral artery and those due to venous congestion of the lower extremities. The blood flow disturbances are frequently associated with DM and hemodialysis. The affected site is reddish purple in color, and the risks of infection developing and spreading are increased by tissue disturbances (ischemia, necrosis, etc.).

Lymph flow insufficiency, due to stenosis (narrowing) and occlusion of the lymphatic vessels of the lower extremities, is also a risk factor. Since tissue fluid and lymph are retained, rather than flowing, elimination of bacteria is disturbed and immunological competence thereby decreases, and complement deficiency and so on are also recognized [1]. Attention should be paid to the possibility of latent lymphedema. Once an infection develops, lymph retention is accelerated and worsens [2, 3].

Causative bacteria

In general, resident flora of the skin, i.e., aerobic Gram-positive cocci (coagulase-negative *Staphylococcus aureus*,

Table 1 Definitions of mild, moderate and severe foot infections

Mild	Extremely localized cellulitis and superficial abscess
Moderate	Cellulitis of a relatively wide-ranging area caudad from the knee
Severe	Cellulitis of a wider ranging area craniad from the knee, spread of inflammation to deep soft tissue
	Abscess of the deep tissue
	Rapidly expanding cellulites
	Dermal necrosis
	Association of lymphangitis
	Systemic inflammatory response syndrome (SIRS)

α-hemolytic *Streptococcus*, *Corynebacterium* species, etc.), frequently cause infections in healthy persons, but these infections are mild. In the presence of abnormalities including rough skin, veroderma (severe dry skin), and chapping and in the presence of the aforementioned risk factors, aerobic Gram-positive cocci with high toxicity (*S. aureus*, β-hemolytic *Streptococcus*) and aerobic Gram-negative bacilli (*Enterobacteriaceae*, etc.) are likely to be isolated [4–6]. Severe infection is associated with adverse host conditions (mixed infections with resistant bacteria including MRSA and *Pseudomonas aeruginosa* and tissue necrosis) in the long-term course of the infection and during the use of antimicrobial agents, leading to isolation of anaerobic bacteria (polymicrobial infections) [7, 8]. In DM patients the rate of isolation of anaerobic bacteria is as high as 74–95% [8, 9]. Many patients with anaerobic isolates have polymicrobial infections (Table 2) [9], and the isolation rate is 35–85% [10–15]. The total number of bacterial species (including aerobes) per specimen is as large as 4.1–5.8. Of the anaerobic bacteria, Gram-positive bacteria are predominantly *Peptostreptococcus* species, *Finegoldia* species, *Parvimonas* species and *Anaerococcus* species, and Gram-negative bacteria predominantly *Bacteroides* species and *Prevotella* species. The type and frequency of the isolates are similar to those for children (pediatric cases) as well [16].

Antimicrobial therapy

Empiric therapy

When a foot infection develops, it is first treated empirically. On this occasion, the selection and method of antimicrobial drug use vary with the severity of the infected lesion.

Table 2 Isolates from infectious lesions of the foot in diabetic patients

Bacterial species	The number of isolates
Aerobic bacteria	607
Gram-positive bacilli	402
Staphylococcus aureus	113
Streptococcus species	97
Enterococcus species	73
Coagulase-negative *Staphylococcus*	66
Other Gram-positive cocci	21
Gram-positive rods	32
Gram-negative bacilli	205
Proteus species	46
Enterobacter species	27
Escherichia coli	25
Klebsiella species	21
Pseudomonas aeruginosa	20
Other Gram-negative rods	64
Gram-negative cocci	2
Anaerobic bacteria	278
Gram-positive bacilli	155
Peptostreptococcus species, *Finegoldia* species, *Parvimonas* species, *Anaerococcus* species	114
Clostridium species	22
Other Gram-positive cocci	19
Gram-negative bacilli	109
Bacteroides fragilis group	45
Other *Bacteroides* species, *Prevotella* species	54
Other Gram-negative anaerobic bacteria	10
Uncategorizable anaerobic bacteria	14
Total	885

Modified from Ref. [9]

Mild

Oral antimicrobial agents with a narrow spectrum are administered for aerobic Gram-positive cocci, particularly targeting *S. aureus*.

In the presence of risk factors such as DM, antimicrobial agents (fluoroquinolones), exerting actions on aerobic Gram-positive cocci and aerobic Gram-negative bacilli, are administered [17].

Moderate

Oral antimicrobial agents (fluoroquinolones, CLDM) [4, 8, 18] are administered, or antimicrobial agents are intravenously injected for a short time (1–7 days), and thereafter

the patient is switched to oral drugs. As antimicrobial agents for intravenous injection, the following are selected: cephamycins, oxacephems and β-lactamase inhibitor combination drugs and carbapenems [19–21]. Moderate cases are treated on an outpatient basis, as a rule, but if the occasion demands, on an inpatient basis.

Severe

Antimicrobial agents are administered intravenously for inpatient treatment. Some β-lactams, i.e., carbapenems, cephamycins, oxacephems, and β-lactamase inhibitor combination drugs [19–21], or fluoroquinolones [18, 22] are selected as antimicrobial agents. The former four drugs are used in the presence of systemic symptoms and for wide-ranging infectious lesions. When the infection is extremely severe, each drug is administered 3–4 times a day. Each of fluoroquinolones is administered twice a day.

Some reports have shown the frequency of anaerobe isolation to be increased during treatment. It is therefore important to select antimicrobial agents, which exert adequate antimicrobial activity against anaerobic bacteria from the beginning of the treatment [9].

Particular attention is needed for patients with risk factors, partly because localized symptoms progress to systemic symptoms within several hours and partly because they are likely to have an early onset of worsening infection severity because of the association of disseminated intravascular coagulation (DIC).

Implementation of bacterial culture

Tissue and pus specimens are collected, and blood is cultured, depending on the situation. In the presence of retention of pus and necrotic tissue and in the absence of clinical efficacy, bacterial collection is necessary. When no pus is obtained by puncture aspiration, it is desirable for specimens to be collected from the margin of the infected lesion [23]. Samples should be collected from the deepest possible layer, because samples from the shallower layers may have been contaminated and the bacterial species actually necessitating treatment cannot always be collected. In the case of collecting anaerobic bacterial specimens particularly, they must be collected from the deepest feasible layer.

Changes in antimicrobial agents

In the case of uncontrollable infection

When an infection shows no indications of amelioration after 3–7 days of antimicrobial agent administration or when the infected lesion expands despite 2–3 days of antimicrobial agent administration, the drugs must be changed to other agents.

In the case of inappropriate antimicrobial activity of drugs identified by bacterial cultures and susceptibility tests

On the basis of results of bacterial cultures and sensitivity tests, appropriate antimicrobial drugs are selected. However, in many patients who have moderate or more severe infections, these infections are likely to be mixed [10–15]. Therefore, antimicrobial drugs that cannot be broken down by β-lactamase are selected.

Administration period of antimicrobial agents

In general, the administration period is 1 week for mild cellulitis [24], and at least 1–2 weeks are needed for moderate or more severe cases [4]. If clinical relief is not recognized, the antimicrobial drugs are to be changed to another type, with continued treatment taking into consideration bacteria which are resistant to the antimicrobial drugs used. An adequate administration period is essential for patients with risk factors because they are apt to suffer recurrences [4].

Necessity of surgical treatment

The necessity of surgical treatment must always be taken into consideration. In the presence of pus retention, drainage is conducted. In the presence of ischemic tissue, debridement is required because not only do antimicrobial agents fail to adequately penetrate tissue but the tissue itself also constitutes an infected lesion. Local rest and cooling are, of course, needed to treat infections, and in extremely severe cases oxygen under high pressure (OHP) therapy and administration of a granulocyte colony-stimulating factor (G-CSF) preparation may also be needed [25].

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